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09/245,198	02/05/1999	JEFFREY BROWNING	A003	4642

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/245,198	BROWNING ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-53,62-78,80-88,91-93,96-98 and 100-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *48,49,64,78,80-84,86-88,93 and 96-98* is/are allowed.

6)☐ Claim(s) *50-53,62,63,65-77,85,91 and 100-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *102605* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The previous Action issued 9/26/05 is withdrawn in favor of the following Action which is NON-FINAL. This Action is issued because the previous Action indicated both that it was a FINAL action, and that it was a NON-FINAL action. This Action is non-final due to a new ground of rejection of claims 75-77, not necessitated by Applicant's amendment.

An amendment was received on 6/27/05.

Claims 54-61, 79, 89, 90, 94, 95, and 99 were canceled, and claims 100-114 were added as requested.

Claims 48-53, 62-78, 80-88, 91-93, 96-98, and 100-114 are pending and under consideration.

An information disclosure statement was received and entered on 7/6/05.

The Declaration of Jeffrey Browning received 6/27/05 has been considered.

Claim Objections

Applicant's amendments were sufficient to overcome the previous grounds of objection for claim misnumbering, improper multiple dependence, and grammar. However, the amendment to claim 85 introduces a space between the word "polypeptide" and the comma immediately following it, deletion of the space is suggested.

Comment

In the Examiner's opinion, use in the claims of the phrase "C-terminal fragment of

SEQ ID NO:4" instead of the phrase "N-terminal truncation of SEQ ID NO:4" would be preferable. As discussed below, in claims drawn to an "N-terminal truncation" it may not be clear whether Applicant is claiming an N-terminal fragment of SEQ ID NO:4, or a C-terminal fragment of SEQ ID NO:4.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50, 85, and 91 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 50 and 91 are ambiguous in the use of the term "amino terminal truncation". It is unclear if the claims are drawn to an N-terminal fragment of SEQ ID NO:4, or to a C-terminal fragment of SEQ ID NO:4. In other words, the claims could be interpreted as embracing a nucleic acid encoding a peptide that is formed by truncating SEQ ID NO:4 at any one of amino acids 81-139, but it is not clear if the claimed polypeptide is the N-terminal or C-terminal truncation fragment. It is also unclear as to which fragment, N-terminal or C-terminal, comprises the amino acid at the point truncation occurs. For example, if truncation occurs at position 81, is amino acid 81 in the C-terminal, or the N-terminal fragment? It is suggested that the claims should be rewritten to be drawn to a substantially pure nucleic acid encoding a fragment of the polypeptide of SEQ ID NO:4, wherein the C-terminus of the fragment is at position 284

of SEQ ID NO:4, and the N-terminus of the fragment is at any one of amino acids 81-139 of SEQ ID NO:4.

In contrast, claims 49 and 92 are considered to be definite because the claimed "amino terminal truncation" consists essentially of amino acids 36-284 of SEQ ID NO:4. Because position 284 is a the C-terminus of SEQ ID NO:4, one can only interpret the claims as being drawn to the C-terminal fragment, and not to the N-terminal fragment.

Claim 85 is indefinite because it recites "said polypeptide produced" without antecedent basis. There is no step in the method in which a polypeptide is produced.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 50 and 91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 50 and 91 can be interpreted in two ways, both of which are new matter. In one interpretation the claims are drawn to a nucleic acid encoding an N-terminal fragment of SEQ ID NO:4 wherein the C-terminus of the fragment is at any one of positions 81-139 of SEQ ID NO:4. There is no support in the specification as filed for

this embodiment. In another interpretation, the claims are drawn to a nucleic acid encoding a C-terminal fragment of SEQ ID NO:4 in which the N-terminus of the fragment is at any one of amino acids 82-140 (i.e. the portion removed from the N-terminus has a C-terminus at one of positions 81-139 of SEQ ID NO:4). There is no support in specification as filed for a C-terminal fragment of SEQ ID NO:4 with an N-terminus corresponding to position 140 of SEQ ID NO:4.

Written Description

Claims 51-53, 62, 63, 65-74, 100-110, and 112-114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 51 and 52 and dependents are drawn to nucleic acids encoding polypeptides that are at least 90 or 95% identical, respectively, to SEQ ID NO:4. SEQ ID NO:4 comprises a human TRELL polypeptide. It is unclear what is the N-terminus of the polypeptide, but it may be at position 1 or position 36 of SEQ ID NO:4. See e.g. page 14, lines 32 and 33. Claim 53 and dependents are drawn to a nucleic acid that hybridizes under high stringency conditions to bases 106-852 or 241-852 of SEQ ID NO:3. SEQ ID NO:3 is a nucleic acid encoding SEQ ID NO:4.

The specification discloses SEQ ID NO:3, a full length cDNA encoding human

TRELL (SEQ ID NO: 4), and SEQ ID NO:1, which is a partial cDNA encoding a fragment of mouse TRELL (SEQ ID NO:2).

The specification discloses at page 36 that human TRELL has the property of inducing apoptosis in HT-29 cells. The specification fails to provide any guidance as to the relationship between the structure of TRELL and this function or any other possible functions such as receptor binding, stimulation of cell proliferation, or alteration of immune response. In particular, there is no guidance as to how the sequence of the disclosed species of the claimed genus can be varied while still retaining any function, and no specific examples are given of any such variant. In view of the large number of conceivable variants in the claimed genus, the disclosure of only a single full length human cDNA and a partial mouse cDNA, and the failure to provide any correlation between the structure of TRELL and any function, one of skill in the art could not conclude that Applicant was in possession of the claimed genus at the time of filing.

Response to Arguments

Applicant's arguments filed 6/27/05 have been fully considered but they are not persuasive.

With regard to claims 51, 52, and dependents, Applicant argues at pages 14 and 15 of the response that because the specification discloses two amino acid sequences (human and mouse) that are less than 90% identical, Applicant was in possession of a genus that is much broader than the claimed genus (i.e. sequences 90% identical to SEQ ID NO:4). Applicant also notes that it is the Examiner's burden to present a

preponderance of evidence why a skilled artisan would not recognize that Applicant was in possession of the claimed genus. The Examiner met this burden by pointing out that the specification provides no guidance as to the relationship between the structure of SEQ ID NO:4 and any function. As discussed at page 11 of the previous Action mailed 1/25/05, the specification teaches that SEQ ID NO:4 is a member of the family of TNF-related cytokines. This family comprises at least 9 different receptor-ligand pairs that have an amino acid sequence-relatedness of about 50%. These molecules have disparate functions ranging from stimulation of apoptosis to stimulation of cell division. The specification gives general guidance as to broad structural features of the prior art molecules, e.g. transmembrane domains, extracellular and intracellular domains, and a cysteine-rich ligand binding domain that is formed through oligomerization of subunits. However, no guidance is offered relative to what specific amino acids are required for any particular function. It is also worth noting that SEQ ID NOS: 2 and 4 differ from the prior art polypeptides in that they do not appear to have any cysteine-rich ligand binding domain, so it is unclear if they form oligomers as do other family members. Further, the specification discloses that the ligands for SEQ ID NOS: 2 and 4 are unknown, as are their biological functions. See e.g. sentence bridging page 4 and 5. Although the specification demonstrates that human TRELL can induce apoptosis in HT-29 cells, it fails to teach what amino acids are required for this or any other function, or what amino acid substitutions will preserve this or any other function. In view of the variety of

structures and functions within the TNF-related cytokine family, and the lack of guidance regarding the structure and function of SEQ ID NOS: 2 and 4, it is highly unpredictable as to how amino acid substitution will affect the functions of SEQ ID NOS: 2 and 4.

Applicant asserts that alignment of SEQ ID NOS : 2 and 4 shows that the human sequence and partial mouse sequence are 88% identical, and have 27 mismatched positions of which 7 are deemed conservative and 20 deemed non-conservative. Applicant argues that these 27 sites represent sites that are likely to tolerate either conservative or non-conservative substitutions. However, the assumption that any of the 27 differing positions is available for substitution without affecting function is invalid because the functions of these residues in each of the proteins is unknown. In fact it is not even known if the mouse and human proteins have the same function. Because the mouse and human versions of TRELL are non-identical, it is possible and likely that their functions are non-identical. The observed amino acid variations could be essential for binding interactions that are critical to function. Even if the mouse and human TRELL homologs bind to homologous receptors and/or effector proteins, it is likely that these receptors or and/or effector proteins have different sequences in the two species, and it is possible that sequence divergence between SEQ ID NOS: 2 and 4 accounts for the ability to recognize these divergent structures. If so, then which amino acids can be changed and which cannot? The specification provides no guidance in this matter, and it is not clear that the mismatched residues can be substituted one for the other while maintaining the known apoptotic function of the human protein or any of the unknown functions of the mouse and human proteins. In view of the diversity of functions in the

TNF-related cytokine family, the divergence in sequence between the human and mouse TRELL sequences does not support claims to a broad genus of variants.

Applicant addresses the rejection of claims 53 and dependents at pages 15 and 16 of the response.

Applicant reiterates the arguments made in support of claims 51 and 52. These arguments are unpersuasive for the reasons set forth above. Applicant also argues that there is adequate written description for the claimed genus because the recited hybridization conditions define a particular genus of structures. For support, Applicant relies on Example 9 of the Written Description Guidelines, and the findings of the court in Enzo Biochem, Inc. v. Gen-Probe Inc. The court referred to Example 9 of the Guidelines. Applicant's arguments are unpersuasive because the situation in Example 9 is not analogous to the instant situation. Example 9 presents a claim drawn to an isolated cDNA that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth under SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity. Thus the protein encoded by the claimed nucleic acid must have a specific function, i.e. it must bind to a specific receptor and induce a specific activity. In contrast the rejected claims identify no specific receptor or activity. Note that the functions recited in claim 62 (binding to a cell surface receptor; having cytokine activity; forming a beta sheet; and altering an immune response) are so general as to be almost meaningless. Again, no specific receptor is defined; "cytokine activity" is extremely broad and encompasses directly opposite activities such as inducing cell division and

apoptosis; "forming a beta sheet" is a structural and not a functional limitation; and "altering a local immune response" entails opposite functions such as enhancing and repressing immune response. As such there is no correlation between the claimed structure and any function, and the claims fail to satisfy the written description requirement. Moreover, the court in Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004) stated that a "patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated." In this case, there is clearly unpredictability associated in the relationship between protein structure and function, as discussed above and below, and the specification fails to describe any amino acid position that is, or is not, required for any function.

Scope of Enablement

Claims 51-53, 62, 63, 65-74, and 100-114 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid molecules encoding SEQ ID NOS:2 or 4 or fragments thereof that induce apoptosis in HT-29 cells, for isolated host cells comprising these nucleic acids, and methods of expressing SEQ ID NOS: 2 and 4, or fragments thereof that induce apoptosis in HT-29 cells, does not reasonably provide enablement for nucleic acid molecules encoding variants of SEQ ID NOS:2 or 4 which comprise one or more amino acid substitutions relative to SEQ ID NOS: 2 and 4, or methods of using those proteins. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 51-53, 62, 63, 65-74 and 100-114 are drawn to nucleic acids encoding variants of the polypeptides of SEQ ID NO: 4. SEQ ID NO:4 comprises the amino acid sequence of human TRELL. The recited variants may be 90% or 95% identical to SEQ ID NO: 4 or particular fragments thereof. See e.g. claims 51, 52, 62, 63, and 65-74. Alternatively the claimed nucleic acids may hybridize to nucleic SEQ ID NOS: 3 under particular highly stringent conditions. See e.g. claims 53, 62, 63, and 65-74. Thus the claims embrace nucleic acids encoding polypeptides that may vary substantially from the disclosed amino acid sequences of SEQ ID NO:4.

The specification teaches the polynucleotides of SEQ ID NOS 1 and 3, which encode amino acid sequences of SEQ ID NOS: 2 and 4. SEQ ID NO:2 comprises the amino acid sequence of a fragment of mouse TRELL, whereas SEQ ID NO:4 comprises full-length human TRELL. SEQ ID NO:2 is homologous to residues 60-284 of SEQ ID NO:4 (See Fig. 1). The specification also teaches the construction of a form of human TRELL lacking the transmembrane region of TRELL, and consisting of some fraction of the extracellular TRELL domain linked to a secretion signal and a myc epitope tag. See pages 34 and 35. The Declaration of Jeffrey Browning, field 6/27/05, provides evidence that this form of human TRELL comprises amino acids 100-284 of SEQ ID NO:4. The specification discloses that human TRELL causes apoptosis in HT-29 cells, but not in several other tumor lines. See page 36 and Table 11 on page 37.

A sequence alignment performed by the PTO showed that SEQ ID NO:1 had

extended regions of high homology with SEQ ID NO:3, such that these nucleic acids would hybridize under the conditions recited in claim 53.

Pertinent to the variant forms of TRELL encompassed by the rejected claims, the specification teaches at page 1 that the family of TNF-related cytokines comprises at least 9 different receptor-ligand pairs that have an amino acid sequence-relatedness of about 50%. These molecules have disparate functions ranging from stimulation of apoptosis to stimulation of cell division. The specification gives general guidance as to broad structural features of the prior art molecules, e.g. transmembrane domains, extracellular and intracellular domains, and a cysteine-rich ligand binding domain that is formed through oligomerization of subunits. However, no guidance is offered relative to what specific amino acids are required for any particular function in these or the claimed molecules. It is also worth noting that SEQ ID NOS: 2 and 4 differ from the prior art polypeptides in that they do not appear to have any cysteine-rich ligand binding domain, so it is unclear if they form oligomers, or if they do, what residues are required for this function. Further, the specification discloses that the ligands for SEQ ID NOS: 2 and 4 are unknown, as are their biological functions. See e.g. sentence bridging page 4 and 5. Although the specification demonstrates that human TRELL can induce apoptosis in HT-29 cells, it fails to teach what amino acids are required for this or any other function, or what amino acid substitutions will preserve this or any other function. In view of the variety of structures and functions within the TNF-related cytokine family, and the lack of guidance regarding the structure and function of SEQ ID NOS: 2 and 4, it is highly unpredictable as to how amino acid substitution will affect the functions of SEQ ID NOS:

2 and 4. The prior art teaches generally that the effects of amino acid substitutions and deletions on protein function are highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) taught that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study." Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) taught that "(i)t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". One might argue that it would not be undue experimentation to express and assay polypeptides individually, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to **known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. Taken together, the teachings of the prior art indicate that substitutions in SEQ ID NOS: 2 and 4 may produce inactive, proteins, and that the functions of altered versions of SEQ ID NOS: 2 and 4 are highly unpredictable. Because the effects of alterations to SEQ ID NOS:2 and 4 are unpredictable, and

because the specification fails to teach which specific alterations can be made without abolishing TRELL activity, one of skill in the art could not make the claimed nucleic acids, other than those encoding polypeptides comprising SEQ ID NOS:2 or 4, or active fragments thereof without undue experimentation.

Response to Arguments

Applicant's arguments filed 6/27/05 have been fully considered but they are not persuasive.

Applicant addresses the enablement rejection at pages 16-19 of the response.

Applicant asserts that claims 51 and 52, which require at least 90% amino acid sequence identity, do not allow substantial variation from SEQ ID NO:4. This is a matter of semantics, still the Office holds that a difference of 5 or 10 amino acids per 100 amino acids can eliminate activity of a protein and therefore can be viewed as a substantial variation.

Applicant asserts in the paragraph bridging pages 16 and 17 that the hybridization language recited in claim 53 does not embrace substantial variation, but defines a very limited and permissible level of variation. Applicant relies for support on the findings of the court in Enzo Biochem, Inc. v. Gen-Probe Inc, which Applicant characterizes as finding that hybridization under high stringency is a condition that dictates that all species within the genus will be structurally similar. This argument is unpersuasive because the claims recite structural limitations at the level of the polypeptide, and hybridization guarantees structural similarity only at the nucleic acid

level, and not at the polypeptide level. For example, a hybridizing nucleic acid can be 99% percent identical to SEQ ID NO:3, but if it contains a frameshift mutation in the second codon, then it does not encode a polypeptide with any structural or functional resemblance to SEQ ID NO:4. The specification as filed does not teach how to use proteins arising from any of the multitude of frameshift or nonsense mutations embraced by the claims.

The remainder of the response is directed to the unpredictability of amino acid substitutions. Applicant argues at page 17 that because SEQ ID NO:2 differs from SEQ ID NO:4 at 27 residues the specification teaches multiple examples of amino acid substitutions produced by natural evolution that are likely to be tolerated in SEQ ID NO:4. This argument was addressed above as follows. The assumption that any of the 27 differing positions is available for substitution without affecting function of SEQ ID NO:4 is invalid because the functions of these residues in each of the proteins is unknown. In fact it is not even known if the mouse and human proteins have the same function. Because the mouse and human versions of TRELL are non-identical, it is possible and likely that their functions are non-identical. The amino acid variations could be essential for binding interactions that are critical to function. Even if the mouse and human TRELL homologs bind to homologous receptors and/or accessory proteins, it is likely that these receptors and/or accessory proteins have different sequences in the two species, and it is possible that sequence divergence between SEQ ID NOS: 2 and 4 accounts for the ability to recognize these divergent structures. If so, then which amino acids can be changed and which cannot? The specification

provides no guidance in this matter, and it is not clear that the mismatched residues can be substituted one for the other while maintaining the known apoptotic function of the human protein or any of the unknown functions of the mouse and human proteins because the specification provides no guidance as to which amino acids are critical for any function. In view of the diversity of functions in the TNF-related cytokine family, the divergence in sequence between the human and mouse TRELL sequences cannot be construed as supporting claims to a broad genus of variants.

At page 17, Applicant argues against the relevance of the Ngo reference to amino acid substitutions in SEQ ID NO:4 by indicating that skilled readers of the application do not need to predict the structure of TRELL proteins because the application teaches that these proteins are TNF family members with two antiparallel beta pleated sheets with a Greek key topology.

This is unpersuasive for at least two reasons. First, the Ngo reference was relied upon to show that the effects of protein structure on protein function are unpredictable in general. Applicant has not shown otherwise, and the specification as filed provides no guidance as to the effects of any single substitution in SEQ ID NO:4. Second, the mere fact that TNF family members have a Greek key topology is insignificant in view of the fact that the members of the TNF family have such diverse sequences and functions, e.g. some members induce cell proliferation whereas others induce apoptosis. If the Greek key topology supports apparently opposite functions, then what can one deduce about the significance of that topology to any specific function of SEQ ID NO:4? Which

amino acids can one change, and how, while still maintaining the function of SEQ ID NO:4?

At pages 18 and 19 Applicant rebuts the relevance of the Rudinger reference to protein structure function relationships, relying on Bowie et al (1990). Applicant's argument is staked on the observation by Bowie that Miller et al (J. Mol. Biol. 131: 191-218, 1979) studied approximately 1500 single amino acid substitutions at 142 positions of the lac repressor, and found that about one half of all substitutions were phenotypically silent. See Bowie at page 247, column 2, first full paragraph. Applicant then presumes that the other half of the mutations had an effect ranging from slight to complete abolishment of activity, and concludes that one can expect to find that over half of random substitutions in any given protein to result in proteins with full or nearly full activity. In fact, the Miller reference does not support this position. Miller generated over 300 altered lac repressor proteins carrying known amino acid substitutions by employing a combination of non-sense mutations at 90 positions of /ac/ with eight different nonsense suppressors. See abstract. By combining various suppressor tRNAs charged with various amino acids, a wide variety of substitution mutations could be obtained. However, the actual amino acid sequence of each mutant repressor was not known because no amino acid or nucleic acid sequencing was performed. The position of each substitution was inferred by foreknowledge of the particular nonsense mutant used. As a result, it was unknown whether or not the sequences of the starting material lacI genes were identical, or if any secondary compensatory mutations occurred during expression of the suppressor mutants. There is no mention in Miller of the 1500 single

amino acid substitutions cited by Bowie, there was no way to assess the possible contribution of compensatory second site mutations, and the relationships between the sequences of the various starting material genes was unknown. As a result, there is inadequate basis for Applicant's argument that the effects of amino acid substitutions are predictable.

Even if Bowie simply erred in referencing Miller and there is another publication with the data cited by Bowie, this data would apply only to single amino acid substitutions. The lac repressor is 360 amino acids long (see Miller (1979) at e.g. page 192, line 3 of second full paragraph), so a repressor with a single amino acid substitution is 99.67% identical to wild type. In contrast, the instant claims are drawn lo polypeptides of as little as 90% identity, i.e. having 30 times as many substitutions and/or insertions and/or deletions per unit length as the single site lac repressor mutant. Clearly, the example referred to by Bowie is not analogous in scope to that of the instant invention, and cannot be considered persuasive regarding the effects of multiple simultaneous mutations on protein structure and function.

In the paragraph bridging pages 18 and 19, Applicant argues that the odds that a single site mutant will be functional are far better than those that were at issue in *In re Wands*. However, as discussed above, the cited art does not support Applicant's deductions regarding the likelihood of retaining functionality, and in any event the claims are not limited to the single site mutations considered by Applicant. In *Wands*, the court found that it was not undue experimentation to screen tens of thousands of hybridomas for a single monoclonal antibody because such was routine in the art at the

time of the invention. There is no evidence of record that it was routine in the art at the time of the invention to screen large numbers of mutants for TRELL activity, and the specification discloses no high throughput assay for detecting such claimed activities as binding to an unidentified cell surface receptor, cytokine activity, forming a beta sheet, or altering an immune response, even though the number of variants embraced by the claims is immense. The claims allow as much as 10% of the 284 amino acids of TRELL to be altered simultaneously. If one made each of the 19 possible substitution mutations at each of the 28 allowed positions (10% of 284 being 28.4), that would be 28^{19} substitutions, otherwise expressed as greater than 3×10^{26} substitutions. That figure only accounts for the number of mutations possible at a single combination of 28 sites, and does not even account for the astronomical number of combinations of 28 or less mutated sites that are possible in a protein of 284 amino acids. There is no evidence of record to indicate that screening that number of mutants is routine in the art, particularly when no particular cell surface receptor or alteration in immune response has been attributed to any version of the claimed protein. In summary, the situation in *Wands* is not analogous to the instant situation.

For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 75-77 are rejected under 35 U.S.C. 102(b) as being anticipated by Shirai et al (US Patent 4921698).

Claims 75-77 are drawn in part to methods of expressing a polypeptide in an animal cell by introducing into the cell a nucleic acid encoding a polypeptide of SEQ ID NO:4. Because the claim recites "a polypeptide of SEQ ID NO:4" it embraces methods of producing any polypeptide sequence of SEQ ID NO:4, including methods of producing a polypeptide comprising a polypeptide fragment of SEQ ID NO:4.

Shirai taught a method of expressing in a mammalian cell a polypeptide comprising the sequence QDP (Gln Asp Pro). See column 1, lines 10-15; column 2, lines 41-50, especially lines 47 and 48; sentence bridging columns 2 and 3; and column 3, lines 3-10.

This rejection can be overcome by substituting --the-- for "a" in the phrase "a polypeptide of SEQ ID NO:4".

Conclusion

Claims 48, 49, 64, 78, 80-84, 86-88, 93, and 96-98 are allowable.

Claim 92 is objected to as depending from a rejected claim, but would be allowable if rewritten as an independent claim incorporating all of the limitations of the claims) from which it depends.

At page 19 of the response Applicant indicated that that the Examiner's remarks in the Reasons for Allowance of 4/26/04 are considered by Applicant to be consistent

with the view that the claims are enabled for uses other than those identified in the reasons for allowance. The Examiner does not share this view.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Richard Schnizer, Ph.D.